REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. CLAIM STATUS & AMENDMENTS

Claims 1-19 were pending in this application when last examined and stand rejected.

Claims 1-4 are amended along the lines suggested at page 3 of the Office Action to replace the term "medicine" with "pharmaceutical composition" for the sole purpose of using more conventional language. This amendment is a non-limiting and is not intended to narrow the scope of protection. Claim 1 is further amended to include "a pharmaceutically acceptable carrier as suggested at page 3 of the Office Action. Support for such amendments can be found throughout the disclosure, for example, at page 13, lines 5-30, and original claims 1-4.

Claim 1 is further amended to incorporate the subject matter of claim 5. Further support can be found in the disclosure, for example, at page 12, lines 22-26, and original claims 1 and 5.

Claims 2-4 are further amended to use more conventional terminology, including "wherein" clauses. These amendments are not intended to narrow the scope of protection. Support can be found in original claims 2-4.

Claims 5-7 and 9-19 are canceled without prejudice or disclaimer thereto. Applicants reserve the right to file a continuation or divisional on any canceled subject matter.

Claims 1-4 and 8 are pending upon entry of this amendment.

The Specification is amended at pages 4 and 13 to include appropriate sequence identifiers for the recited amino acid sequences along the lines at page 12, lines 25-26. Support can also be found in the Sequence Listing as filed. No new matter has been added.

The Specification is amended at page 22, lines 25-26, to correct a typographical error by referring to the appropriate Fig. No. No new matter has been added.

II. INFORMATION DISCLOSURE STATEMENT

Attached herewith is an English translation of reference AH (Kondoh) listed in the PTO-1449 Form submitted with the IDS of April 28, 2005. Please consider this reference and return an Examiner-initialed PTO-1449 Form indicating such. A courtesy copy of the PTO-1449 Form submitted with the IDS of April 28, 2005 is attached herewith for the Office's convenience.

III. OBJECTIONS TO THE SPECIFICATION

The Specification was objected for containing minor informalities for the reasons set forth in items 2-3 on page 2 of the Office Action (e.g., omitting appropriate SEQ ID NOS for recited sequences and for referring to incorrect Figs.).

Applicants respectfully submit that the present amendment overcomes these objections. Specifically, the Specification has been amended at pages 4 and 13 to include appropriate sequence identifiers for the recited amino acid sequences along the lines at page 12, lines 25-26. The Specification is amended at page 22, lines 25-26, to refer to the correct Fig. No. along the lines suggested in item 3 on page 2 of the Action. Therefore, please withdraw the above-noted objections.

IV. OBJECTION TO THE CLAIMS

Claims 6, 7, 9, 10 and 14-19 were objected to for omitting appropriate SEQ ID NOS for recited sequences.

The present amendment cancels these claims, thereby obviating this objection.

V. ENABLEMENT REJECTION

In item 5 on page 3 of the Office Action, claims 1-7 and 11-19 were rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification is not enabled for the full scope of the claimed invention.

Applicants respectfully traverse this rejection as applied to the amended claims.

First, it is noted that independent claim 1 has been amended along the lines indicated as enabled in item 5 on page 3 of the Office Action. Specifically, amended

claim 1 calls for a pharmaceutical composition comprising a mutant of an angiotensin-converting enzyme (ACE) and a pharmaceutically acceptable carrier. The mutant has GPI-anchored protein releasing activity and is the ACE consisting of a substitution of Glu by Asp in the zinc binding sequence of His-Glu-Met-Gly-His of SEQ ID NO: 4, and releases GPI-anchored protein from the cell surface. Support for the mutant ACE of SEQ ID NO: 4 with Glu at position 414 substituted with Asp can be found in the disclosure, for example, at page 12, lines 11-26. The Specification also discloses common and routine procedures for preparing pharmaceutical compositions containing the mutant ACE of the present invention. See, for instance, at page 13, line 5 to page 14, line 13.

Accordingly, the amended claims no longer refer to any angiotensin-converting enzyme (ACE) containing medicine, of which action mechanism is release of GPI-anchored protein from the cell surface.

Second, Applicants respectfully traverse the Office's alleged lack of enablement for treatment of a specific disease condition. According to the Office, the Specification is only enabled for suppressing accumulation of beta amyloid protein as indicated in the prior art. This is incorrect. The Specification discloses the relationship between a GPI-anchored protein and various disease conditions. See, for instance, the disclosure at page 1, last paragraph, to the third paragraph on page 2. In this regard, it is well known that the GPI-anchored protein is main component of cell membranes (and binds there by a GPI-anchor) and is crucial for many biological processes. The Specification discloses that the normal prion protein binds the GPI-anchor on cell surfaces, and when the pathogenic form of prion binds to the normal counterpart, it results in prion-related diseases, such as Creutzfeldt-Jakob disease, Gerstmann-Straussele syndrome and kuru disease, etc. See, the disclosure at page 1, line 29, to page 2, line 2. The Specification, at page 2, lines 2-4, also teaches that the bacterial toxin lipopolysaccharide (LPS) exhibits cytotoxicity and binds to its receptor CD14, which is also a GPI-anchored protein. The Specification discloses that when sperm binds to the zona pellucida of eggs, GPI-anchored proteins (e.g., PH-20 and TESP5) should be released from the sperm surface otherwise male infertility can occur. See page 2, lines 6-8.

Please also see Kondoh et al. (Nature Medicine, Vol. 11, No. 2, pp. 160-166, February 2005), reference AO, submitted in the IDS submitted August 8, 2005. In this

reference, it is disclosed that the relationship between GIP-anchored protein and some diseases had been well known at the time of the present invention. Accordingly, it was common knowledge at the time of the present invention that release of GPI-anchored protein from cell surface is effective for preventing and curing prion-related diseases, bacterial infectious diseases and male infertility due to sperm abnormality.

Please also note the effect of ACE in curing male infertility due to sperm abnormality as shown in Example 2-5 on pages 23-24 of the Specification. As described at this location, the most prominent phenotype of ACE-knockout mice is male infertility. Compared with wild-type sperm, ACE knockout sperm exhibited defective sperm-egg binding at the zona pellucida. In Example 2-5, it is disclosed that: (1) treatment with peptidase-inactivated ACE vigorously restored the sperm-zona binding defect of ACE knockout mice (Figs. 18 and 19); and (2) PI-PLC treatment cured the egg binding ability of ACE knockout sperm. The results of Example 2-5 confirm that GPIase activity of ACE is crucial for the ability of sperm to bind to eggs.

Based on such disclosure and the knowledge in the art, Applicants respectfully submit that the skilled artisan, would reasonably find credible the disclosed relationship between a GPI-anchored protein and the disclosed disease conditions. Further, the skilled artisan, upon reading the disclosure and in view of the knowledge in the art, could make and use the claimed pharmaceutical composition to treat and/or prevent prion-related diseases, bacterial infectious diseases and male infertility due to sperm abnormality without undue experimentation.

Therefore, Applicants respectfully submit that the above-noted enablement rejection is untenable and should be withdrawn.

VI. WRITTEN DESCRIPTION REJECTION

In item 6 on page 7 of the Office Action, claims 1-7 and 11-19 were rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification lacks written description support for the claimed invention.

Applicants respectfully submit that the present amendment overcomes this rejection for the reasons noted above.

Amended claim 1 is directed to the mutant ACE exemplified in the disclosure. Specifically, claim 1 calls for a pharmaceutical composition comprising a mutant of an angiotensin-converting enzyme (ACE) consisting of the amino acid sequence of SEQ ID NO: 4 except Glu at position 414 is substituted with Asp. Support can be found in the disclosure, for example, at page 12, lines 11-26. Accordingly, the amended claims no longer refer to any and all ACE variants. Thus, the above-noted written description rejection should be withdrawn.

VII. INDEFINITENESS REJECTION

Claims 1-7 and 11-19 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the reasons in items 8-9 on page 9.

Applicants respectfully submit that the present amendment overcomes this rejection.

To start, the claims have been amended to include the full name for the abbreviation "GPI" at its first appearance in the claims to address the concern in item 8.

Also, dependent claims 2-4 now further limit the recited use in the preamble of amended independent claim 1. This addresses the concern in item 9.

Thus, the above-noted indefiniteness rejection should be withdrawn.

VIII. PRIOR ART REJECTIONS

On page 10 of the Office Action, claims 1-4 were rejected under 35 U.S.C. § 102(a) as anticipated by Ko et al. (JP 2001-316287, published November 13, 2001, English Abstract).

On page 10 of the Action, claims 8-10 were rejected under 35 U.S.C. § 102(b) as anticipated by Wei et al. (J. Biol. Chem., vol. 266, pp. 9002-9008, 1991).

On page 11, claims 8-9 were rejected under 35 U.S.C. § 102(b) as anticipated by Jaspard et al. (J. Biol. Chem., vol. 268, pp. 9496-9503, 1993).

On page 11, claim 8 was rejected under 35 U.S.C. § 102(b) as anticipated by Sen et al. (J. Biol. Chem., vol. 268, pp. 25748-25754).

Applicants respectfully submit that the present amendment overcomes the above prior art rejections. None pf the cited references disclose or suggest a mutant of an

angiotensin-converting enzyme (ACE) consisting of the amino acid sequence of SEQ ID NO: 4 except Glu at position 414 is substituted with Asp, wherein said mutant has GPI-anchored protein releasing activity as in the present invention. Since the cited references fail to disclose or suggest this element of the claimed invention, the references cannot anticipate the invention.

Therefore, the above-noted prior art rejections are untenable and should be withdrawn.

IX. CONCLUSION

In view of the foregoing amendments and remarks, that the present application is in condition for allowance and notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned at the telephone number below.

Respectfully submitted,

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December 28, 2007

ATTACHMENTS

1. English translation of reference AH (Kondoh);
2. Courtesy copy of PTO-1449 Form submitted with the IDS of April 28, 2005.

Isolation and function analysis for a factor releasing GPI-anchored protein from mouse germ cell

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(1) Object

In order to easily detect a localization of GPI-anchored protein, and then to analyze a metabolic mechanism of GPI-anchored protein in vivo, we construct a GPI-anchored GFP reporter protein (GFP-GPI). GFP-GPI was localized at plasma membrane, golgi body, microsome fraction, and lipd raft on membrane surface upon transfecting into cell culture. Introducing in to mouse body, GFP-GPI was localized at the top edge of epithelial tissue and nervous system, from which it was found out that GFP-GPI has various characters of GPI-anchored protein. Further, it was also found out that GFP-GPI was released at exocrine grand and testis more than expected. Thereinafter, we focused its attention on this fact and isolated and analyzed a factor releasing GPI-anchored protein from mouse testis by measuring release of GFP-GPI or placental alkaline phosphatase, a kind of GPI-anchored protein.

(2) Methods and Results

Germ cells fraction was prepared from adult mouse testis, and cell extract was produced under existence of 1% TritonX-100. The cell extract was subjected to various liquid column chromatography columns (anion exchanger column, hydrophobic interaction column, ConA column, gel filtration column) thereby purifying a releasing factor for GPI-anchored protein. As a result of mass analysis, the molecule was revealed to be angiotensin-converting enzyme (ACE). Treating cultured cells (HeLa, F9, HEK293 etc.) with ACE, various GPI-anchored proteins (EGFP-GPI, CD59, DAF, prion protein, Sca-1, Thy-1) were released from cell surface.

(3) Summary and Perspective

It was revealed from the results that ACE has not only dipeptidyl carboxtlpeptidases activity utilizing angiotensin I and bradykinin as a substrate, but also has a novel activity of releasing GPI-anchored proteins from cell surface.

In addition, in GPI-knockout mouse, some phenomenon such as male infertility can't be explained along the line with the previous concept for GPI activity. Consequently, we would re-construct physiological functions of ACE, through a detailed analysis of the activity and identification of GPI-anchored protein for the substrate of ACE in germ cells and vascular endothelial cells.

COPY

JC12 Rec'd PCT/PTO 28 APR 2005

Sheet 1 of 2

INFORMATION DISCLOSURE STATEMENT

FORM PTO 1449 (*modified*)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

LIST OF REFERENCES CITED BY APPLICANT(S)
(*Use several sheets if necessary*)

Date Submitted to PTO: April 28, 2005

ATTY DOCKET NO.	SERIAL NO.
2005_0733A	NEW 10/532986
APPLICANT	
Gen KONDOH	
FILING DATE	**GROUP**
April 28, 2005	

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA						
	AB						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AC	91/354	1/1991	WO				
	AD	2001-316287	11/2001	JP				
	AE	95/32725	12/1995	WO				
	AF							
	AG							

OTHER DOCUMENT(S) (*Including Author, Title, Date, Pertinent Pages, Etc.*)

	AH	H. Kondo, "Mouse Seishoku Saibo GPI Anchor-gata Tanpakushitsu Yuri Inshi no Tanri to Kino Kaiseki", Seishoku Saibo no Seigyo Kiko to Hassei Kogaku, Heisei 11-14, Nendo, No. 11234101, pp. 69-72.
	AI	E. Jaspard et al., "Differences in the properties and enzymatic specificities of the two active sites of angiotensin I-converting enzyme (kininase II). Studies with bradykinin and other natural peptides", J. Biol. Chem., 1993, Vol. 268, No. 13, pp. 9496-9503
	AJ	L. Wei et al., "The two homologous domains of human angiotensin I-converting enzyme are both catalytically active", J. Biol. Chem., 1991, Vol. 266, No. 14, pp. 9002-9008.
	AK	L. Wei et al., "The two homologous domain of human angiotensin I-converting enzyme interact differently with competitive inhibitors", J. Biol. Chem., 1992, Vol. 267, No. 19, pp. 13398-13405.
	AL	S. Pang et al., "Roles of the juxtamembrane and extracellular domains of angiotensin-converting enzyme in ectodomain Shedding", Biochem. J., 2001, Vol. 358, (Pt 1), pp. 185-192.
	AM	B. Maric et al., "Replacement of the transmembrane anchor in angiotensin I-converting enzyme (ACE) with a glycosylphosphatidylinositol tail affects activation of the B2 bradykinin receptor by ACE inhibitors", J. Biol. Chem., 2000, Vol. 275, No. 21, pp. 16110-16118.
	AN	S. Pang et al., "The ectodomain of angiotensin converting enzyme does not dictate sensitivity to sacretase cleavage", Biochemical Society transactions, 2000, Vol. 28, No. 5, p. A262.

EXAMINER	DATE CONSIDERED

*EXAMINER: *Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.*